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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/737,633	11/15/1996	FABRIZIO SAMARITANI	P/42-60	5401

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Edward A Meilman
Dickstein Shaprio Morin & Oshinsky LLP
1177 Avenue of the Americas
41st Floor
New York, NY 10036-2714

EXAMINER	
LANDSMAN, ROBERT S	
ART UNIT	PAPER NUMBER
1647	35

DATE MAILED: 05/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/737,633	SAMARITANI ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4 and 6-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,7,9, 10, 11, 13 and 14* is/are rejected.

7)☒ Claim(s) *8,12 and 15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

AK 4/30/03

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Formal Matters

A. Amendment F, filed 2/20/03, has been entered into the record.

B. Claims 1-10 were pending. In Amendment F, Applicants canceled claims 2 and 5 and added new claims 11-15. Therefore, claims 1, 3, 4 and 6-15 are pending and are the subject of this Office Action.

C. All Statutes under 35 USC not found in this Action can be found, cited in full, in a previous Office Action.

D. While not forming the basis for an objection or rejection, the syntax of claim 12 can be improved. The claim recites "...in which the interferon-beta...is employed." The claim would read more clearly if the claim was amended to either remove the phrase "is employed" and the reword the claim as written in claim 8 using "comprising" language, or to rewrite the claim to recite "...in which conditions comprising interferon-beta at 1 MIU/ml, mannitol at 54.6 mg/ml...are employed."

2. Specification

A. The specification is objected to since the continuing data (i.e. reference to this application being a 371 of PCT/EP95/01825) is not recited in the first line of the specification.

3. Claim Objections

A. As stated in the "Conclusion" section of this Office Action, claim 8 remains objected to for the reasons already of record on page 2 of the Office Action dated 9/27/02, but would be allowable if rewritten in independent format to include the limitations of the claims from which they depend.

B. As stated in the "Conclusion" section of this Office Action, claims 12 and 15 are objected to since they depend from rejected base claims, but would be allowable if rewritten in independent format to include the limitations of the claims from which they depend.

4. Claim Rejections - 35 USC § 103

A. Claims 1, 3, 7, 9 and 10 remain rejected under 35 USC 103(a) as being unpatentable over Hanisch et al. (U.S. Patent No. 5,643,566) in view of Hershenson et al. (U.S. Patent No. 5,004,605) for the reasons already of record on pages 2-4 of the Office Action dated 9/27/02. These claims are further rejected in view of Cymbalista for the reasons already of record on page 5 of the Office Action dated 9/27/02. Applicants have amended claims 1 and 9 to contain the limitation of an acetate buffer originally recited in cancelled claim 5. Applicants did not specifically address the issues found in this rejection (paragraph 3A) and only stated that "while the rejections set forth in the claim rejections paragraph 3A and 3B are clearly moot in light of the foregoing amendment, it would appear that a rejection under 35 USC 103 over Hanisch in view of Hershenson and Cymbalista remains to be addressed. However, since Applicants have combined the limitations of claim 5, which are pertinent to Cymbalista et al. as seen in paragraph 3C on page 5 of the Office Action dated 9/27/02, Applicants arguments will be addressed below.

Applicants argue that the remarks by the Board, which vacated the appeal and remanded the case to the Examiner on May 23, 2002 did not reflect many of the observations made by Applicants in their present response, dated 2/20/03. Applicants argue that Hanisch et al. teach two distinct IFN formulations and that the description of a pH 2-4 liquid formulation containing interferon-beta optionally a stabilizer which possibly is mannitol is the relevant teaching as it pertains to the present invention. Applicants argue, according to Hanisch et al., that for low pH formulations, PPF is preferred as a stabilizer over albumin to produce a very clear interferon-beta material since the quantity of albumin required to produce this same material is high. This argument has been considered, but is not deemed persuasive. Hanisch et al. only teach that PPF is *preferred*, but still teach that albumin can be used as a stabilizer. In fact, PPF is composed of at least 83% albumin (column 9, lines 44-46). Regardless, Hanisch et al. still meet the limitations of claim 1 of the present invention.

Applicants also argue that, while Hanisch et al. teach the use of buffers during the recovery of recombinant proteins, they do not teach a liquid pharmaceutical composition containing interferon-beta, mannitol, a buffer and, optionally, albumin. This argument has been considered, but is also not deemed persuasive. The rejection of these claims of the present invention, respectfully, fall under the realm of obviousness. Therefore, the reference(s) does not have to teach every element of the claim(s), but only must make obvious the claimed invention. However, as recited on pages 3-4 of the Office Action dated 9/27/02, Hanisch et al. do teach pharmaceutical compositions comprising IFN-beta, mannitol and albumin (column 5, lines 6-50; column 9, lines 17-52). Though Hanisch et al. do not specifically teach the use of a buffer in a pharmaceutical composition, not only would the artisan immediately envision the use of a

buffer in the preparation of a pharmaceutical composition, but it would have been obvious at the time of the invention to have used a buffer in order to maintain the pH of the solution, especially if the pharmaceutical composition was to be stored. Pharmaceutical compositions are not used immediately upon preparation, but are normally stored, shipped, or sold. Therefore, any liquid pharmaceutical composition must be buffered. In fact, Hanisch et al. teach that "carbohydrate stabilizers can only be used in formulations maintained/lyophilized at pH 2-4" (column 9, lines 51-52). It would be obvious that a buffer could be used to maintain this pH. In addition, if the composition was lyophilized, the composition would need to be resuspended prior to use. Therefore, it would also have been obvious to the artisan at the time of the present invention to have resuspended this composition/formulation using a buffer, or water, as required since lyophilized solutions are not suitable for pharmaceutical use. Furthermore, this rejection relied on Hershenson et al. as a secondary reference and, as stated by Applicants on page 6 of this response, dated 2/20/03, Hershenson et al. do teach the use of buffers in their pharmaceutical compositions (column 9, lines 5-20).

Applicants also argue that Hershenson et al. teach that any formulation comprising INF-beta, mannitol and a buffer at a pH of 2-4 must comprise either glycerol or PEG polymers and that the present claims exclude these components. Again, this rejection must be read in light of both primary and secondary references. Though Hershenson et al. may not teach a pharmaceutical formulation in the absence of glycerol or PEG polymers, they do not teach that these components are required. However, Hanisch et al. do teach pharmaceutical formulations at a pH of 2-4 in the absence of glycerol, or PEG polymers. Therefore, when Hershenson et al. is read in light of Hanisch et al., it can be concluded that glycerol or PEG polymers are not required. This same logic can be used when considering claims reciting the use of acetate buffer. Applicants argue that Cymbalista only teaches the use of acetate buffer with PVP, which is not recited in the current claims. However, there is nothing in Cymbalista which shows, or suggests that PVP is a requirement and that acetate buffer would not be suitable in the absence of PVP. Cymbalista only teaches that some stabilization is required. As seen in this rejection, mannitol can be used as a stabilizer. Therefore, given the well-known use of acetate buffer in the art, the artisan would have had a reasonable expectation of success in using acetate buffer in the absence of PVP, or with another stabilizer, in absence of evidence to the contrary.

Applicants also argue that the outstanding results found in Tables I-III of the specification, along with the Declaration of Dr. Esposito, which is already of record, make the present invention unobvious. The Declaration of Dr. Esposito has, respectfully, already been significantly analyzed and commented on in the Final rejection mailed 9/11/98 (Paper No. 14). The major argument against the Declaration and

Applicants present arguments is that, as stated on page 2 of the Final rejection of Paper 14, the claims do not require any particular degree of stabilization other than effective "stabilizing." It is believed that all pertinent arguments have been addressed.

B. Claims 4 and 6 remain rejected under 35 USC 103(a) and new claims 11 and 14 are also rejected under 35 USC 103(a) as being unpatentable over Hanisch et al. (U.S. Patent No. 5,643,566) in view of Hershenson et al. (U.S. Patent No. 5,004,605) for the reasons already of record on pages 4-5 of the Office Action dated 9/27/02 as well as for the reasons stated above (paragraph A) under 35 USC 103. These claims are further rejected in view of Cymbalista for the reasons already of record on page 5 of the Office Action dated 9/27/02. Applicants have amended claim 1 to contain the limitation of an acetate buffer originally recited in cancelled claim 5. Claims 4 and 6 depend from claim 1. New claim 11 also depends from claim 1, whereas new claim 14 depends from claim 11. Applicants did not specifically address the issues found in these claims and only stated that "while the rejections set forth in the claim rejections paragraph 3A and 3B are clearly moot in light of the foregoing amendment, it would appear that a rejection under 35 USC 103 over Hanisch in view of Hershenson and Cymbalista remains to be addressed. Therefore, there is nothing new for the Examiner to address. However, regarding claim 14, though neither Hanisch et al. nor Hershenson et al. teach that the containers of their invention are hermetically sealed (i.e. under sterile conditions), it would have been obvious to the artisan to use these conditions since the formulations in these containers were to be used for pharmaceutical use and sterility is a requirement for pharmaceutical compositions.

5. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claims 13 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims, which are product claims, depend from claims 11 or 12, both of which are process claims.

6. Conclusion

A. Claims 1, 3, 4, 6, 7, 9, 10, 11, 13 and 14 are rejected.

B. Claims 8, 12, and 15 are objected to, but would be allowable if rewritten in independent format to include the limitations of claim 1 and/or claim 9.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
April 30, 2003

ROBERT LANDSMAN
PATENT EXAMINER